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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,401	02/27/2007	Seth Hallstrom	16785.10	8352

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/599,401	HALLSTROM ET AL.
	Examiner	Art Unit
	SAMUEL LIU	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/18/11 & 5/12/11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 7 and 14* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In response to the pre-appeal conference request filed by the applicant on 7-18-11, a pre-appeal conference was held on 8-4-11 and the examiner was directed to reopen the prosecution of this application.

The amendment filed 5/12/11 (after finality) which amends claim 1 has been entered. The following 103 rejection is based on this amendment (see below). Claim 3 was cancelled by the amendment filed 3/16/10; and claims 4-6, 8-13 and 15-18 were cancelled by the amendment filed 9/30/10. Claims 1, 2, 7, and 14 are under examination.

The 112/2 rejection of claims 1, 2, 7 and 14 set forth in the Office action mailed 3/16/11 is withdrawn in light of the amendment of claim 1.

New-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schlag et al. (US Pat. No. 6358918 B1) or Hallstrom et al. (2002) *Circulation*, 105, 3032-3038) in view of Demopoulos et al. (US 2002/0136763 A1) or/and Lipton S. A. (UA Pat. No. 6525017 B1).

Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (*plurality*) thiol-group containing protein (claim 16); wherein at least 95% or 90% of the thiol groups of said protein are nitrosated, i.e., S-nitrosated protein (claims 19 and 20), and wherein said "at least one thiol-group containing protein" that has been nitrosated is S-nitroso-albumin (claim 21), as applied to claim 1.

Schlag et al. teach that, in their invention the "mixtures" of nitrosated proteins or proteins capable of being nitrosated (i.e., proteins that have not been nitrosated and still have free thiol groups) is particularly preferred (col.2, lines 58-60). This suggests that, in addition to the nitrosated protein, e.g., "S-nitroso-albumin" (S-NO-albumin), any other protein(s)/peptide(s) (in agreement with the above-discussed "*plurality*") which potentially could include GSH) that contains free thiol groups can be combined with the S-NO-albumin.

Schlag et al. further teach that the thiol-group containing protein has N-nitrosation, O-nitrosation and/or C-nitrosation level of less than 10% (patent claim 24), and S-nitrosation level of at least 95% or 90% (patent claims 19 and 20), as applied to instant claims 2, 7 and 14 herein.

Hallstrom et al. also teach the use of S-nitrosated human serum albumin (S-NO-HSA) to treat ischemic condition, i.e., ischemia/reperfusion injury of skeletal muscle in a rabbit (seethe entire document).

Yet, neither Schlag et al. nor Hallstrom et al. expressly teach combination of the S-NO-albumin with the reduced glutathione (GSH) for treating ischemia.

However, Demopoulos et al. teach glutathione can be used in combination with other therapies (i.e., suggesting the combination with **other therapeutic agents** or proteins) for treating free radical associated disorders, e.g., ischemic event (see [0115], lines 1-3 and 6). Alternatively, Lipton also discloses a method of treating patients with nervous system ischemia by administering to said patient a pharmaceutical composition comprising reduced glutathione GSH (see patent claims 3 and 4).

With the teachings of the above references in hand, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S-nitroso albumin (S-NO-HSA) and GSH for treating the ischemia. This is because Schlag et al. teach the benefits of treating ischemia using S-NO-albumin, and that it is particularly preferred to use "mixtures" (combination) of nitrosated proteins for example "S-NO-albumin" with "any other proteins/peptides" containing free thiol groups wherein said any other proteins/peptides could potentially include GSH. Hallstrom et al. also teach that GSH has the capability of scavenging superoxide (O_2^-) that causes the tissue ischemic damage. Because of this well known teaching in the prior art it is also arguable that one of ordinary skill in the art would have chosen GSH as one of said "any other proteins/peptides" in the "mixtures" taught by Schlag et al..

Further, Demopoulos et al. have also taught a feasibility of combining glutathione with other "therapeutic protein(s)/peptide(s)" for treating therapies (i.e., suggesting free radical associated disorders, e.g., ischemia (see above). Here, glutathione is considered to be one of said "therapeutic protein(s)/peptide(s)" (see [0001], Domopoulos et al.). Upon reading the above

references, one of ordinary skill in the art would have readily realized the benefits of including the GSH along with the nitrosated albumin in the treatment of ischemia, not only due to the capability of GSH in scavenging superoxide that causes tissue ischemic damage as taught by Hallstrom, but also, due to the fact that GSH has been demonstrated to be therapeutically active in treating ischemia (see the Lipton's US patent and Demopoulos's teaching above).

Based on the above discussed motivations, one of ordinary skill in the art would have readily added GSH to the formulation of S-NO-albumin, e.g., S-NO-HAS, with GSH, and would have used said formulation to treat ischemia with reasonable expectation of success. Therefore a combination of the teachings of either Schlag/Hallstrom and Lipton or Schlag/Hallstrom and Demopoulous renders the claimed method *prima facie* obvious.

The applicants' response to the 103(a) rejection above

In the "*pre-appeal brief conference and panel review*" filed 7/18/11, applicants submit that Hallstrom et al. do not teach/suggest administration of GSH to a patient for treating ischemia but rather teach S-NO-HSA alone for ischemia treatment, since GSH exists naturally in body (p.4, lines 5-8). The applicants argue that S-BNO-HSA is highly effective already; hence, administration of both S-NO-albumin and GSH is not obvious, and asserts that administering two compounds (S-NO-albumin and GSH) would require greater expenditure of time, effort, or resources compared to administering one compound (p.5, 1st paragraph).

The applicants' arguments are not persuasive because of the reasons set forth in the above new 103(a) rejection, and the reasons below. Although Hallstrom et al., which has taught use of S-NO-HAS to treat the ischemic condition in rabbit, do not expressly teach use GSH with the S-NO-HAS, Demopoulos et al. or/and Lipton have taught the therapeutic feasibility of using GSH to treat ischemia. In addition to this, Demopoulos et al. have taught that GSH can be combined with other therapeutic protein for the ischemia treatment (see above 103 rejection). The reason for GSH is said "therapeutic protein" has been discussed in detail in the body of the rejection. One of ordinary skill in the art would have readily known that said other therapeutic protein is S-NO-albumin, because, like GSH, in the same line, the ability of S-NO-albumin to treat ischemia has been shown by Domopoulo et al. or/and Lipto.

Consistent with this, the primary reference Schlag et al. has taught the particularly preferred combination ("mixture") of the nitrosated protein (S-NO-protein) with "any other protein/peptide" having free thiol groups; said "mixture" is used as a pharmaceutical preparation (col.2, lines 5152 and 58-60) for treating ischemia disclosed in the patent claims 16-21 of Schlag et al. (see corresponding section in the above 103 rejection); wherein it can be argued that it would be obvious to one of ordinary skill in the art to conclude that said "any other protein/peptide" could potentially include GSH in view of the teachings of Demopoulos or/and Lipton to treat ischemia. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S-nitroso albumin (e.g., S-NO-HSA) and GSH for treating the ischemia..

In addition, applicants argue the unexpected results via discussion of Examples 1-3 (see p.6, 1st paragraph), and infer that the unexpected results show objective evidence of non-obviousness of the claimed method (p.6, last paragraph).

The Example 1, 2 and 3 show a drop in blood pressure, an increase in NO release and a drop in platelet aggregation, respectively, when S-NO-albumin and GSH is administered. However, none of these examples provide any factual evidence as to why such events are unexpected or beneficial. Even otherwise, in view of the combined teachings of the above references such events would be inherent to the method and expected by one skilled in the art. Also, in view of the above combined teachings of the references a synergistic effect of GSH and the S-NO-albumin in treating ischemia when compared to treatment with GSH alone or with S-NO-albumin alone would be expected by one skilled in the art. Thus, Examples 1-3 are not considered to have provided the convincing unexpected results to sufficiently establish the asserted non-obviousness; and therefore, the 103(a) rejection stands.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
August 4, 2011

/Manjunath N. Rao /
Supervisory Patent Examiner, Art Unit 1656